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MERCK
Research Laboratories

RE: [Docket No. 00D-0186]
Draft Guidance: M4 Common Technical Document

Merck & Co., Inc, is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $2 Billion, annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market, today.

Research, by its nature, is a multidisciplinary and highly risk-intensive business. It depends upon many variables, including: prolific source materials, first class talent, adequate funding, efficient and effective quality processes and procedures, and a predictable regulatory environment.

Merck's research scientists ensure that our Research process continues to identify medically important product candidates from thousands of chemical and molecular entities screened, each year. Only one in ten of these research product candidates is selected to enter the Development testing programs. The medicines which Merck ultimately presents to worldwide health authorities for marketing approval are those that have met the highest technical standards available and those that are able to withstand the most critical regulatory review.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

Merck has participated with health authorities from around the globe in the harmonization of regulatory standards under the auspices of the International Conference on Harmonization (ICH). The objectives of ICH have been to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical products caused by incompatible regulatory schemes. We continue to monitor the equitable and consistent application of these harmonized standards to product development in order to ensure that *new* or *improved* therapies reach patients as swiftly as possible.

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In the course of bringing our product candidates through developmental testing and clinical trials, Merck scientists regularly identify and address issues affected by this proposal. Indeed, we submit numerous original and supplemental New Drug Applications annually which contain documentation addressed in the Draft Guidance. For these reasons, we are very interested and well qualified to comment on this Draft Guidance.

We commend the FDA as well as all ICH participants in their pursuit to harmonize and streamline documentation requirements for marketing applications for human use. Merck has a number of comments and questions which we feel help to clarify the current draft guidance.

General Comment

The amount of cross-referencing or repetition of information across the quality, safety, and efficacy modules seems excessive and may extend the length of time required to prepare the dossier, since most documents are written independently of each other. Considering the pending availability of ICH M2 [Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI)], Merck recommends consideration of the advantages and the inherent functionality of electronic submissions which may enhance navigation through documents, rather than requiring mandatory cross-references throughout the dossier.

Specific Comments

A. Safety - Modules IIA and IIB

Module IIA

1. The Draft Guidance states that the Nonclinical Executive Summary should note "any association between findings and the quality of the human pharmaceutical, the results of clinical trials, and effects seen with related products should be indicated". Due to the fact that the nonclinical results are typically available much earlier than the clinical results, this requirement will make it very difficult for sponsors to finalize any documentation for a marketing application until after all results are available. Merck recommends that this position be further discussed in the context of the availability of ICH M2 [Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI)]. The facilitation of electronic navigation may preclude the need to discuss this association in the Executive Summary.

2 The Draft Guidance states: "Nonclinical testing strategy should be discussed." Does this require more or different information than what is already provided in the rationale currently included in the Pharmacology section? Merck recommends that this section and the Content and Structural Format section should be clarified if new information is required to explain nonclinical testing strategy.

3. The Draft Guidance states: "Except for biotechnology-derived products, an assessment of the impurities and degradants present ...". It is important to Merck (and other vaccine & /or biologicals manufacturers) that this guidance be extended to traditional biologic products as well. However, since it is not possible to identify, purify, characterize, and then perform preclinical studies on all potential biological byproducts that may be present in trace amounts, Merck recommends that this sentence be changed to: "Except for biotechnology-derived products *or other biological products produced by traditional means*, an assessment of the impurities and degradants present ...".

4. The Draft Guidance suggests that recommendations be made for the product label in the Overview and Conclusions of the Executive Summary. Generally specific labeling statements are contained in the proposed labeling supplied with the marketing application. Merck recommends that this new requirement be reconsidered in the context of ICH M2 [Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI)]. The facilitation of electronic navigation may preclude the need to discuss these recommendations in the Executive Summary.

5. Merck recommends limiting the Executive Summary to 15-20 pages as the Written Summaries are 100-150 pages.

6. Merck recommends that the term "pharmacology" be replaced with "pharmacodynamics" when discussing topics within Modules IIA and IIB.

Module IIB1- Nonclinical Written Summaries

1. In Section 2.1, the proposed order of dosage groups is not consistent with the order currently used for human trials. Merck recommends that the Guidance not mandate the order of the groups.

2. Section 2.3 proposes to restrict the length of the nonclinical written summary to 100-150 pages. Because of the possibility of important information being omitted, Merck recommends restricting the length of the Executive Summary to 15 – 20 pages and allowing more flexibility in length of the Written Summary.

3. Section 2.4 states that "discussion relating to the proposed prescribing information is primarily addressed in the Nonclinical Executive Summary". This implies that information may be discussed in the Executive Summary which is not discussed in the Written Summary. Merck recommends that no new information be presented in the Executive Summary that is not already included in the Written Summary.

4. The Draft Guidance implies that Safety Pharmacology will be part of the Pharmacology Section rather than the Toxicology Section. Since these will be the only GLP studies within the Pharmacology Section, that may be appropriate. However, this requirement conflicts with the draft guidelines for Safety Pharmacology (topic S7), where a Safety Pharmacology study can be incorporated into (or be part of) a Toxicology study (e.g. neurological signs assessed in the Acute Toxicology studies could satisfy CNS requirement for Safety Pharmacology). Merck recommends that this requirement be clarified to explain whether or not these studies should be included in both Pharmacology and Toxicology sections.

5. Toxicokinetics is not addressed in the Draft Guidance. Toxicokinetics is usually grouped with the Pharmacokinetics (PK) data in the Tabulated Nonclinical Summaries. Merck experience indicates that toxicokinetic data are generated as part of toxicity studies and therefore, fit more logically in the Toxicology section.

6. The Draft Guidance should clarify whether reference citations are to be made to the Tabulated Summaries and Study/Report number (Table X.X, Study/Report Number) or to a reference number.

7. The Draft Guidance requests cross-referencing to data contained in other sections of the application.. As stated under General Comments above, this complicates preparation of a dossier and may be too awkward and time-consuming to implement into current practice..

8. In Section 3.1, No. 2, it is unclear whether duration "of use" or "of action" is being requested.

9. The Draft Guidance requires a separate discussion of Primary Pharmacodynamics (Section 3.2.2) and Secondary Pharmacodynamics (Section 3.2.3). Since some studies may span categories, it may be difficult to always separate primary and secondary pharmacodynamics. Merck recommends that the Guidance provide for flexibility in this presentation.

10. In the table titled "Model-independent pharmacokinetic parameters...." in Section 3.6, the Dose (mg/kg) row should be moved into the header of the table. The rest of the data in the table (C_{max}, etc.) correspond to data that were collected at the various doses (2, 10, and 30 mg/kg). Also, a t½ is missing and should be included.

11. Generally, in most of the tables and figures in the Draft Guidance, symbols were not used systematically as recommended in writing guides (e.g., AMA Manual of Style). Merck recommends using a standard approach for using symbols that is commonly accepted throughout industry practice.

Module IIB2 - Nonclinical Tabulated Summaries

1. The Draft Guidance requires that representative information on humans at the maximum recommended dose or human data for comparison be included in the PK section,. Merck recommends flexibility in placement of this information. It will be difficult to implement this current practices due to the fact that clinical information is not available until much later than the nonclinical PK information and sponsors will be unable to complete any documentation until the last pieces of data are available. Merck recommends that this issue be reviewed in the context of ICH M2 [Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI)]. The facilitation of electronic navigation may preclude the need to present the human data in the Nonclinical PK section.

1. 2. The Draft Guidance states that the statistical significance of the actual data and not of the percent differences, be used in the Carcinogenicity tabulations and that the sponsor indicate whether or not these data "meets or exceeds guidelines of the EEC and Japan." Neither of these requirements is current practice in industry.. Merck recommends that the rationale for these requests be provided and clarification as to whether or not these statements must be specific or general, in content
2. 3. Ordinarily the organization of Nonclinical Tabulated Summaries will vary considerably depending on the best way to present the data. Each program is likely to be unique and this is usually considered as desirable. Merck recommends that the guidance allow this flexibility.

Module IV - Table of Contents: Organization of Nonclinical Data

1. In Sections B 3.5.2 and 3.5.3, the difference between Fetal and Prenatal development is not clear Is there a gestation period distinction? Merck recommends clarification of this point.

2. Merck recommends that the phrase "where appropriate" be added to Local Tolerance in Section B 3.6.

3. In Section 3.7.3 (Other Toxicity Studies), the Draft Guidance does not state whether or not "Mechanistic studies" are studies that define the mechanism of toxicity. In industry practice, those studies usually appear elsewhere. Merck recommends that the Guidance clarify this.

B. Quality – Module III

General Comments

1. Environmental Assessment is included in both Modules II (Safety) and III (Quality). Merck recommends that, if, in fact, the information required is different for each Module, the information to be provided in each Module be clearly identified so that there is no confusion.

2. Until Harmonization of the Pharmacopeias can be accomplished, a true common document relying on multiple compendia, will not be realized. For example, drug product composition includes the quality of the ingredient. It should be understood that listing multiple compendia such as USP, EP and JP for an individual non-harmonized excipient will require that the European Region only reference the European Pharmacopoeia, the Japan Region only reference the Japanese Pharmacopoeia, and so on. Merck recommends that the Draft Guidance clarify whether or not this is the case or whether separate, region-specific listings will be needed *and* whether this also applies to test methods and packaging components.

3. It is unclear where Investigational Formulations are to be included and whether or not this is another example of region-specific information.

4. The Draft Guidance does not describe how references to Drug Master Files are to be addressed.

Comments on the Table of Contents

1. S1.1 (Nomenclature): The Draft Guidance lists BAN as an example of "other names" used. Since the UK has abandoned the use of BAN and adopts the INN name of a substance, Merck recommends deleting this example.

2. S1.2 (Structure): Merck recommends adding "physical form" as a data module.

3. In Section S2.2, the Draft Guidance describes what is needed for a New Chemical Entity (NCE), as follows, : "the acceptability of this will depend on the level of detail planned for inclusion." Merck recommends that this statement be clarified.

4. In Section S 2.3, there is a subsection entitled: "Additionally, for Biotech products produced from cell banks:" Merck recommends that this be changed to: "Additionally, for Biotech products *or other biological products produced by traditional means that are* produced from cell banks:" for the reason noted above.

5. In Section S2.3, there is a small listing of additional information desired for biotech products. Merck recommends that the following be added to the listing: *"passage history (including propagation conditions, cell lines used, and number of passage)".*

6. In Section S2.4, it is unclear whether the note to add stability supporting storage conditions also applies to non-biotech products.

7. In Section S4.4 on batch analyses, there is a requirement to register a specific batch size. Merck questions the need for this, because, as demand for a product increases, this requirement will force numerous unnecessary updates to the application.

8. In Section S 7.2, the module title is: "Post-approval stability protocol and stability commitment." In most cases, the stability protocol to be followed is an extension of the stability program that is already accruing data, and that has provided the stability data included within the dossier. Merck recommends the title of this module be changed to *"Stability protocol and post-approval stability commitment"*.

9. In Section P1, the same issue of the use of regional compendia is raised if the ingredient monograph is not harmonized.

10. Section P3.5 (Process Validation or Evaluation) Merck recommends a regional approach because the evaluation is not usually complete at filing, nor is the protocol usually filed.

11. Regarding Section P 4.5 (Excipients of Human or Animal Origin) – Merck recommends that the *country of origin* be added to the listing of items for which information should be provided.

12. Regarding Section P7, data are presented after conclusions. Merck recommends reversing the order.

13. To address the requirement for Environmental Assessment and Investigational Formulations, Merck recommends that applicable "Other Information" requirements for submission should be listed along with region, rather than include reference to regional guidelines next to title.

14. Regarding Section A 2 (Viral Safety Evaluation), Merck recommends that an evaluation of the presence/ absence of all adventitious agents be included, not just a status of the presence of viruses because bacteria or virions may also be introduced during the process. Accordingly, Merck recommends that the focus of this section be expanded and re-titled to: *"Safety Evaluation"*.

C. <u>EFFICACY - Module V</u>

1. Including reports on studies investigating related indications and indications other than those proposed would add unnecessarily to the volume of and to the time required to prepare the application. Merck recommends that this requirement be simplified or omitted.

2. It is unclear whether the report for post-marketing experience is to be based on published and/or unpublished information.

3. In Section A (Table of Contents) - For supplements or variations, the Draft Guidance states that the Table of Contents should indicate either 'not applicable' or 'no study conducted'. There will be many situations where that would apply to all but 2 or 3 of the sections which could make the dossier appear deficient. Merck recommends that, for clarity and simplicity, if an entire category is not applicable, then only one statement be indicated on the Table Of Contents at the top level and not repeated for every subsection (e.g. 3.1, 3.2, 3.3, etc.).

4. Section B (Tabular Listing) - it is not clear whether or not this listing would replace the current FDA requirement for a Table of All Clinical Studies or the EU requirement for the Overall Study Summary. The intent without the guideline for the written and executive summaries cannot be determined, so this provision should be clarified.

5. In Section C (Study Reports) - the rationale for this organization is unclear. As a result it is difficult to assess how any sponsor would be able to address this logistically. Numerous studies will belong in multiple categories and it will be confusing unless specific rationale and guidance is provided. Merck recommends that, to allow flexibility to the sponsor, the Draft Guidance provide only a proposed organization. This organization may be used as guidance, but could be altered at the discretion of the sponsor based on the data available. This flexibility will also become necessary when applied to a supplemental application or variation.

6. Merck disagrees with the need to separate Human PK/PD study reports into predefined structured categories since some studies fulfill multiple objectives. The reports should simply serve as references to the summary of PK/PD. With the incorporation of indexing allowed by electronic submissions (within PDF), the reviewer could easily navigate from the integrated summary to the specific reference. ICH M2 [Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI)] may also provide guidance in this area when it becomes available.

7. Regarding Section C.7 on CRT and CRF, organizing the CRT by sections consistent with the Study Reports is acceptable current practice in industry. However, it is not an appropriate system for the CRFs. Merck recommends that CRFs be organized by category (Death, Discontinued, etc.) and then in study order within each category.

We welcome the opportunity to comment on this Draft Guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,

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